

Molecular Diagnostic Laboratory Setup and Maintenance for Sars-Cov-2

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ABSTRACT

Importance of laboratory diagnosis has come to the spotlight once again with the COVID-19 pandemic caused by Sars-Cov-2 and significant changes have taken place in terms of laboratory operation. A global effort has emerged when all healthcare professionals faced a biological threat. Interlaboratory collaboration and multidisciplinary approach contributed to this effort. This study aims to explain step-by-step establishment of a fully capable laboratory for Sars-Cov-2 diagnosis to support local and global fight for the COVID-19 pandemic. Several precautions were taken, and disaster plans were updated because of the changes in employee health and workload distribution. Some of these are setting up a laboratory from scratch for microorganism diagnostic tests performed in pandemic cases, measures for healthcare workers, personnel assignment planning, changes in the variety and number of tests, innovations in quality standards and the contribution of laboratories to scientific studies. Ankara Molecular Diagnostic Laboratory has become one of the laboratories in Türkiye where Sars-Cov-2 and its mutations have been studied the most with 1,710,856 samples between 01 October 2020 and 01 May 2022 since its establishment and it has become the laboratory with the highest number of equipment and technical personnel in the capital. This study summarizes all the phases of Ankara Molecular Diagnostic Laboratory beginning with its establishment from the scratch and covers all the steps to render this facility fully operational.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (Sars-Cov-2), a new coronavirus, emerged in December 2019 in Wuhan, China is the etiological agent of the coronavirus disease 2019 (COVID) which was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 (Tan et al., 2020). More than 532 million confirmed cases of COVID-19 have been reported worldwide with more than six million deaths by the end of March 2022 according to WHO data (WHO Situation Report., 2022). The first COVID-19 case in our country coincides with global pandemic declaration date and health services were significantly affected in the face of this unexpected situation (Finch et al.;2022). The diagnosis of COVID-19 infection caused by Sars-Cov-2 needs to be confirmed by laboratory tests. Reverse transcription and real-time polymerase chain reaction (RT-qPCR) based on the demonstration of Sars-Cov-2 viral RNA is the gold standard in diagnosis (Liu et al.; 2020). Sample collection, transportation and storage are the factors that affect the RT-PCR results mostly. Collecting accurate respiratory tract sample at the right time at the preanalytical stage is very important for an accurate and rapid molecular diagnosis of Sars-Cov-2 (Lippi, 2019). Number of centers performing the COVID-19 tests was increased shortly after the detection of the first case in Türkiye and this number has reached to 528 laboratories today (RTMH, 2022). The pandemic process still continues in the world and in our country. Some of the laboratories activated in this process have been integrated into existing laboratories and some have been established from scratch (WHO Interim Guidance, 2022). Ankara Molecular Diagnosis Laboratory which is the subject of our study is the highest capacity Sars-Cov-2 diagnostic test laboratory in Ankara. It is setup by repurposing emergency department of an old hospital and contains backups of every area.

Healthcare services have been severely affected by the COVID-19 pandemic and states have had to plan and act quickly. A guide titled "GP36-A, Planning Laboratory Operations During Disaster" was published by the Clinical and Laboratory Standards Institute (CLSI) based on previous experience (Williams et al.;

2014). This guideline published prior to the pandemic states that the annual re-emergence of common, severe, and seasonal influenza is a routine expectation. The possibility of the appearance of an unexpected new influenza strain with pathogenic potential has highlighted the need for each laboratory to carefully review its disaster plan periodically. The tests frequently performed during the pandemic are replaced by the intense Sars-Cov-2 diagnosis, follow-up, and screening tests while one-step reverse transcription and real-time polymerase chain reaction (RT-qPCR) based on the detection of mutated regions in viral RNA and Anti-SARS IgG, IgA, IgM tests have outstripped tests for other diseases (Lippi et al.; 2020). This significantly affected laboratory staff distribution, test load of the analyzers and material supply. In some cases, necessities such as kits and consumables and service requests could not be fulfilled (Lippi and Plebani, 2020). Health institution and the patients it served were affected in such situations. Some of the healthcare workers were reluctant to continue their work due to anxiety, some fell ill, and some passed away from the disease during the pandemic. Legal regulations or rewarding initiatives were implemented to prevent loss of personnel workforce and thus ensuring the healthcare service sustainability (Sharma B et al.; 2021, Tahamtan et al.; 2020). Special precautions had to be taken against viral contamination for the health and safety of laboratory workers with the pandemic. There were conflicts about the measures due to the lack of clear viral transmission routes information or data even though provisional guidelines were published at the beginning of the pandemic. Standards were improved with the increase viral transmission route evidences during the pandemic process.

The aim of this study is to evaluate the importance of the Molecular Diagnosis Laboratory which started its activities on October 01, 2020, within the Ankara Public Health, simultaneously authorized as the pandemic laboratory along with the effects on its staff and its operation as an instance of its preparation and setup processes during the pandemic.

MATERIALS AND METHODS

In our study, the preparatory phase in which samples from our laboratory were carried out in the laboratories established to respond to the COVID-19 pandemic, the phase in which the laboratory working system was rearranged, and the management of the personnel and samples were evaluated. COVID-19 (Sars-Cov-2 infection) was evaluated within the scope of contact tracing, epidemic management, patient monitoring at home and sample handling guide while de-identified samples were included in the study within the scope of

routine work by the sample handling teams as a Scientific Advisory Board Study. The study was performed by retrospectively scanning the Laboratory Management Information System (LIMS) of the Ankara Molecular Diagnosis Laboratory after obtaining the approval of permission from Yıldırım Beyazıt University Yenimahalle Training and Research Hospital Ethics Committee (Date: April 13, 2022, and Decision No: 2022-33). The study was in accordance

with the Declaration of Helsinki and its later amendments as revised in 2013.

Statistical analysis

Statistical Package of Social Sciences 22 (SPSS Chicago, IL, USA) software was used for data analysis and Excel was used to draw graphics. Categorical variables were expressed as numbers and percentages. The differences between the ratios were analyzed by Pearson chi-square analysis while $P < 0.05$ was taken as statistical significance level.

Changes in Laboratory Organization

Laboratory Layout and Design

It has been decided to establish Ankara Molecular Diagnosis Laboratory where tests such as RT-qPCR, antigen antibody etc. for Sars-Cov-2 infection diagnosis are planned to be carried out in the emergency services unit of Numune Hospital which has physical and technical infrastructures such as sample reception, staff preparation room, automatic controlled door systems in terms of its layout and design. Personnel preparation areas, rest rooms and laboratory area where the personnel can wear their protective equipment before entering the laboratory have been designed. The Master Mix Preparation Room (Clean room), Extraction room, an Amplification room (Dirty room) and the room where the PCR devices will be placed are built for molecular analysis. It is very

important that pre-PCR activities are separated from the amplification and analysis area as separate rooms or separate benches since there is usually a low amount of nucleic acid sample during preparation and a very high concentration after amplification. This means that false positive results can occur because of amplicon contamination if PCR is analyzed in the same area where the master mix and samples were prepared (Ortiz et al.; 2020).

Personnel working area was also made suitable for these conditions to ensure a one-way workflow. Areas that will enable healthcare professionals to change their personal protective equipment (PPE) since they may be contaminated with amplicon aerosols and intermediate sterilization stations where they can sterilize the PPEs under UV have been created for the personnel if they need to return to pre-PCR area from the amplification and analysis areas (Aberaa et al.; 2020). Since the physical conditions are suitable, these rooms are built with identical couple areas as backup so that the laboratory operations are not interrupted in case of possible contamination. Each room has dedicated special devices, equipment, and consumables. Equipment such as Real-Time PCR device, Biosafety cabinet II, refrigerator, freezer, vortex, and pipette set to be used in the COVID-19 test process and consumables such as pipette tips, Eppendorf tubes, gloves are provided by Ankara Public Health Laboratory. A significant increase in the sample density of the laboratory in 2022 is shown in Fig.1.

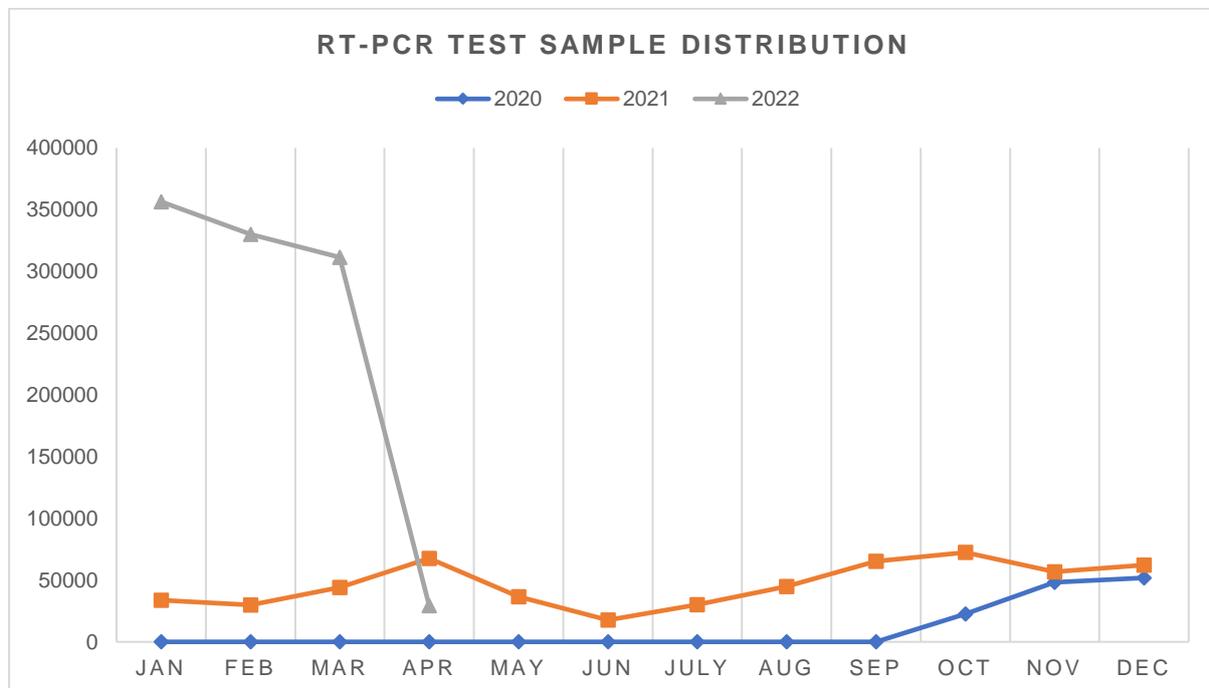


Figure-1 Distribution Chart of the Number of Samples Sent to Ankara Molecular Diagnosis Laboratory from the Day It Was Opened Until April 2022 and the Comparison of the Total Number of Samples.

Measures for Personnel Health

Some international and national guides on personnel health were published and updated at short intervals. Among these, the "Laboratory Biosafety Guidelines for Coronavirus Disease" published by WHO is the most up to date (WHO Interim Guidance, 2022). The purpose of this document is to provide provisional guidance on laboratory biosafety during the analysis of biological materials of COVID-19 patients. Each laboratory should take risk control measures by carrying out an institutional risk assessment to perform their analyses safely according to the guide.

Appropriate personal protective equipment (PPE), determined by a detailed risk assessment, should be used by all laboratory personnel analyzing biological material of COVID-19 patients. All technical procedures should be performed in a way to minimize the generation of aerosols and droplets (van Doremalen et al.; 2020). Appropriate disinfectants with proven efficiency against enveloped viruses (for example, hypochlorite, alcohol, hydrogen peroxide, quaternary ammonium compounds, and phenolic compounds) should be consumed during the recommended contact time, at the correct dilution level and within the expiration date after solution preparation. "Good Microbiological Practice and Procedures" should be followed when processing and analyzing all specimens, for PCR testing (WHO Interim Guidance, 2022). It is stated that the lysis buffer in RNA extraction is effective in inactivating the Sars-Cov-2 virus (CDC 2020). Patient specimens from suspected or confirmed cases should be transported as "Biological Substance - Category B (UN3373)". Viral culture or isolates should be transferred as "Infectious Substance Affecting Humans - Category A (UN2814)" (WHO, 2019). It shows that the Sars-Cov-2 virus may be susceptible to disinfectants [1,000 ppm (0.1%) for general surface disinfection and 10,000 ppm (1%) sodium hypochlorite, 62% 71% ethanol for disinfection of sample spills; 0.5% hydrogen peroxide; biocidal agents such as quaternary ammonium compounds or phenolic compounds] with proven activity against enveloped viruses (Chin et al; 2020). In the interim guide published by WHO it is recommended to use PPE for healthcare professionals according to personnel and type of activity during the care of suspected, probable, and confirmed COVID-19 patients (WHO COVID-19, 2020).

Terms and duration of use, the rules to follow when removing, reusability and risks of PPE are specified in cases where there is a shortage of PPE such as medical masks, FFP2, FFP3, N95, N99, N100 or equivalent respiratory masks, protective clothing, protective glasses, face shield, gloves (COVID-19 Laboratory Biosafety Guide, 2020). It is recommended that medical masks and FFP2, FFP3, N95, N99, N100 or equivalent respirators can be used without removing them for up to 6 hours when dealing with COVID-19

patients and are eventually to be destroyed. FFP1 breathing mask without exhalation valve can be used as an alternative in the absence of a medical mask. It is stated that decontamination processes can be performed using disinfection or sterilization methods for FFP2, FFP3, N95, N99, N100 or equivalent respiratory masks while reuse of medical masks is not recommended. It is not recommended to use a respirator together with a medical mask to prolong its use, alternatively, a face shield should be used (WHO COVID-19, 2020).

Cotton uniforms as protective clothing, reusable (washable) patient or laboratory personnel aprons can be washed with detergent at 60 °C and reused. Disposable laboratory personnel aprons or liquid-proof plastic aprons are recommended as an alternative to these clothes. Disinfection for the reuse of goggles and face shields that fully cover the eyes can be used. Cleaning with soap/detergent and water, followed by 0.1% sodium hypochlorite (pursued by rinsing with water) or a 70% alcohol wipe respectively is recommended for disinfection. Safety glasses that partially cover the eyes as an alternative to goggles and transparent binding sheets with rubber bands that can be designed by the personnel as an alternative to the face shield can be used. The use of double gloves and repeated use of the same gloves are not recommended unless surgical intervention is required.

A provisional guide for the laboratory operations has been published by the national health administrators in our country (COVID-19 Laboratory Biosafety Guide, 2020). It is recommended to have separate clothes or uniforms and to wear shoes or closed slippers, and not to go home with these clothes. Uniforms should not be hung in the same place (hanger, closet) as other daily clothes and personnel should refrain from going to resting areas with aprons. It is recommended not to consume food and beverages outside the rest areas. The rest room and technical areas with windows should be ventilated periodically. WHO recommends 6-12 air changes per hour by opening doors and windows in healthcare environments where there are most likely viral load-bearing particles. It is recommended to use "suction mode" and avoid recirculation of air when using the air conditioner (WHO,2020).

It is recommended not to allow anyone other than the personnel to enter the laboratory and to apply the social distance rule by using a security strip in the sample reception unit. Disinfectant should be provided to all rooms, including the rest room, offices and technical rooms, and its use should be encouraged. Personnel meals can be served as disposable rations (COVID-19 Laboratory Biosafety Guide, 2020). Wastes belonging to a possible and identified COVID-19 patient in the laboratory environment where Sars-Cov-2 test is studied should be considered as infectious waste and disposed of as medical waste in accordance with guidelines (Waste Management in the COVID-19 Pandemic, 2022).

Challenges Faced by Laboratory Staff in the COVID-19 Pandemic

Personnel were transferred from other national health institutions/hospital due to the need for experienced technicians for Sars-Cov-2 PCR analysis. Increase in the anxiety and uneasiness of contracting the disease in our country caused some health personnel to retire or resign in this process. Laboratory professionals were assigned to non-laboratory sampling units to collect naso-oropharyngeal swab. Staff lost their motivation and anxiety were created because of these assignments that were not within the scope of their training (Blasco-Belled et al.; 2022). Effective training and competency assessment programs ensure that the personnel are knowledgeable and competent for the task assigned to them and in their responsibilities according to CLSI's guideline "QMS03, Education and Competence Assessment" (CLSI guideline QMS03, 2016)

In this guide, it is recommended the personnel have the necessary knowledge, skills, and behaviors to fulfill their duties and tasks assigned to them with high quality along with a consistent and predictably high performance. Administrative leave was given to personnel who are older (60 and over), pregnant, have cancer, have a disability report, and have chronic diseases in our laboratory. In addition, number of personnel working in laboratory was minimized to reduce the risk of contamination. Personnel were divided into teams and worked in shifts to reduce the number of tests, viral load, and exposure. Laboratory technicians were trained to use more than one device or system. However, workload per staff increased despite the rapidly decreasing test load. Laboratory specialists were assigned to outpatient clinics or wards where the COVID-19 patient diagnosis and follow-up outside the laboratory is carried out.

Personnel assignments and shifts dynamically changed during the pandemic process and these changes were adapted to laboratory conditions. Difficulties were experienced at the beginning of the pandemic due to time constraints, uncertainty, insufficient training, irregularity in personnel employment and long shifts even though incentive extra compensation for

healthcare personnel due to COVID-19 was paid. Information was collected on satisfaction related to institutional policies implemented during the epidemic including providing PPE, sanitation practices, additional transport arrangements and education with a survey (n=64) of medical laboratory specialists in a developing country [25]. 68% of the participants stated that they were generally satisfied with the measures taken by the institution to deal with the crisis. 56% of the participants were satisfied with the timely, appropriate, and adequate PPE supply and 88% with the general cleaning practices. 18% of staff believed that previous training was lacking to effectively confront the pandemic except 7 unbiased responses. Only 34% of the personnel thought that transportation to/from health institution was sufficient even though ease of transportation is provided for employees to use. Many staff felt significant anxiety and worry as they could carry the virus home (Jafri et al.;2020).

Innovations in Quality Standards

Sars-Cov-2 is considered a Group 4 biological factor that causes severe human diseases, poses danger to employees, has a high risk of spreading to the community but does not have effective prevention and treatment methods. Each laboratory should conduct its own risk analysis within the scope of exposure to the agent and prevention of risks for this reason corrective and preventive measures should be taken in the action plan to reduce the risk. New documents and instructions related to COVID-19 or updates to existing ones should be made in health facilities in accordance with the quality standards in health. "Laboratory Operating Procedure" in our laboratory was updated and new documents such as "COVID-19 Pandemic Preparation and Action Plan", "Highly Infectious Patient Sample Instructions", "Cleaning and Disinfection Recommendations and Products to be Used in Possible/Definite Cases of COVID-19", "Recommended Personal Protective Equipment for COVID-19 Disease and Its Use" and "Occupational Health and Safety Unit COVID-19 Instructions" were introduced.

RESULTS

Sars-Cov-2 RT-qPCR test was performed on 1,710,856 patient samples between October 01, 2020, and May 01, 2022, in our laboratory. 47.5% belonged to female patients and 52.5% to male patients while the median age was determined as 48.0 (age range 1–98) among these samples. When the sample amount rates based by months in 2021 for our laboratory which was opened in November 2020 after being authorized by the Ministry

of Health were compared, it was seen that there was an increase in April and October ($p < 0.01$; from 50.1% to 66.8%) while the total number of applications for April 2022 was found to be significantly decreased ($p < 0.01$; from 49.9% to 33.2%). 68.9% are under 50 years old, 19.6% are between 50-64 years old, 11.5% are over 65 years old and the median was 40.0 (age range 18-96) when the age groups are examined.

CONCLUSIONS

All laboratory professionals have demonstrated an extraordinary effort despite the lack of human and technical resources and gained experience in crisis management. This crisis has proven once again that laboratory medicine is central to clinical decision-making. Therefore, health policy makers and institution management should plan further laboratory discipline more reasonably. The importance and value of laboratories which are not only in the diagnosis of the disease but also in the prognosis and treatment follow-up should be conveyed to the senior management. The medical laboratory community should convene and share information with each other, communicate with clinicians and strive to work in a multidisciplinary manner.

Since we must live with the pandemic for a while, resources should be invested into mobile laboratories

equipped with the necessary devices and equipment along with trained personnel to support local testing operations to prevent health system and laboratory services from overloading and even collapsing in extreme conditions. Current diagnosis and risk estimation conditions should be improved with the identification of new biomarkers specific to the infectious agent. More reliable epidemiological studies should be performed, and the accessibility of these kits should be increased with the availability of licensed test kits and standardization of test protocols. Hygiene rules should be imposed as an indispensable part of our lives in terms of employee health to prevent personnel workforce and regrettable healthcare professional demise.

DISCUSSION

Personnel duties and authorizations should be defined, and it should be determined by whom the relevant process will be managed during the crisis. Mental, social, and economic needs of the personnel should be considered and the efforts to meet these requirements should be standardized to provide sustainable and high-quality performance. Progress will be achieved in processes to determine which individual is infected in the short term and to monitor the progression of the disease while determining vaccine effectiveness to be developed in the long term with the developments in laboratory medicine. Several contributions can be made to virus research, drugs and vaccines development, service and resource management in health centers and mobility analysis to predict and manage scenarios arising from health problems with artificial intelligence projects based on data science.

In the COVID-19 pandemic which affected the whole world, we were faced with the stages of establishing a laboratory from scratch because of the insufficient number of laboratories for Sars-Cov-2 diagnosis in our country. In general, the inconvenience of physical

conditions, small laboratory spaces, insufficient and inappropriate consumables, lack of competent technical personnel to work in the laboratory and long bureaucratic processes in personnel recruitment were the limiting factors in the first place. Pandemics are unpredictable situations. There is a need for multidisciplinary management systems that can make and implement rapid decisions by coordinating the laboratories where the tests in which gold standard tests in diagnosis are carried out to manage disasters such as the COVID-19 pandemic. Most of the Sars-Cov-2 research focus on the identification of the virus and the availability of the laboratory facilities, required equipments and trained personnel are taken for granted. Therefore investigations for Sars-Cov-2 specific laboratory requirements and their specifications are quite scarce in the relevant literature. The safety and design considerations of a mobile biocontainment laboratory for COVID-19 outbreak is presented in a research (Linster et al.;2020) but this is a very specific and minimalistic case when compared to a full-scale pandemic laboratory setup and maintenance effort provided in this study.

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Conflict of Interest

The authors report there are no conflicting interests to declare.

Ethical Approval

The study was performed by retrospectively scanning the Laboratory Management Information System (LIMS) of the Ankara Molecular Diagnosis Laboratory

after obtaining the approval of permission from Yıldırım Beyazıt University Yenimahalle Training and Research Hospital Ethics Committee (Date: April 13,

2022, and Decision No: 2022-33). The study was in accordance with the Declaration of Helsinki and its later amendments as revised in 2013.

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